

AMENDMENTS TO THE CLAIMS:

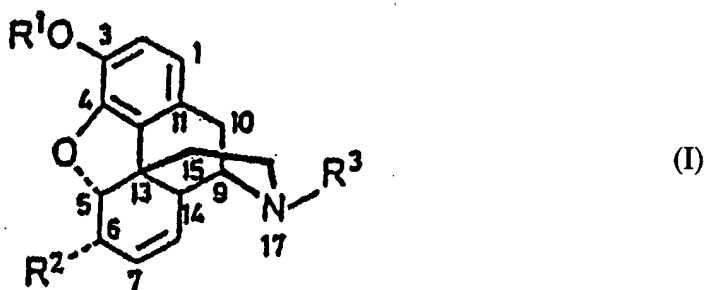
Please replace the claims with the claims provided in the listing below wherein status, amendments, additions and cancellations are indicated.

Claims 1. - 30. - (Cancelled)

Claim 31. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Transdermal
or transmucosal composition for administering at least one morphine alkaloid, the
composition consisting essentially of:

an a morphine acid addition salt, formed by the reaction of:

A) at least one morphine alkaloid of formula I



where R¹ is selected from the group consisting of: H, and C₁ to C₆ alkyl;

R^2 is selected from the group consisting of: H, OH, $OC(O)CH_3$, $=O$, and $=CH_2$, such that when R^2 is H, OH, or $OC(O)CH_3$, a fourth valence bond at the C (6) position in formula I is H;

R^3 is selected from the group consisting of: CH_3 , cyclopropyl, cyclobutyl, and allyl;

the bond between the C (7) and C (8) positions in formula I is alternatively saturated; and

alternatively there is a nitroxyl group at the N (17) position in formula I; with

- B) at least one organic acid selected from the group consisting of:
- a) an acid that is an equilibrium product of a mixture of a monoester of a C_3 to C_{16} dicarboxylic acid and a monohydric C_1 to C_4 alcohol;
 - b) C_2 to C_{16} sulfonic acids;
 - c) a substituted benzoic acid selected from the group consisting of: halogen, hydroxy, alkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, and amino substituted benzoic acid;
 - d) 5- and 6-member ring heterocyclic compounds having at least one N or S atom, with unsaturated and saturated rings, and unsubstituted, and substituted with one of: a carboxyl group,

unbranched and branched carboxypropyl, and unbranched and branched carboxybutyl;

- e) C_5 to C_{10} oxocarboxylic acids, unsaturated and saturated, and unsubstituted and substituted;
- f) phenyl-substituted and phenoxy-substituted saturated C_2 to C_4 carboxylic acids; and
- g) aliphatic, aromatic, and heterocyclic C_2 to C_{12} amino acids, and aliphatic, aromatic, and heterocyclic C_2 to C_{12} (mono) amino acids and (poly) amino acids (polypeptides), wherein at least one amino group is substituted with one of:
 - i) an unsubstituted C_2 to C_6 alkanoyl group,
 - ii) a substituted C_2 to C_6 alkanoyl group,
 - iii) an unsubstituted benzoyl group, and
 - iv) a substituted benzoyl group;

and

one of: a solvent for said morphine acid addition salt, and a suspension medium for said morphine acid addition salt;

said solvent or said suspension medium being selected from the group consisting of: glycerol, ethylene glycol, oleic acid, dimethylisobornide, dimethylsulfoxide, and olive oil.

Claim 32. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said morphine alkaloid is selected from the group consisting of: morphine, codeine, heroin, ethylmorphine, levorphanol, hydromorphone, and mixtures of any of the foregoing.

Claim 33. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said monoester in (B)(1) is of a C₅ - C₁₀ dicarboxylic acid.

Claim 34. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said monoester in (B)(1) is monomethylsebacate.

Claim 35. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said dicarboxylic acid in (B)(1) is selected from the group consisting of: suberic acid, azelaic acid, and sebacic acid.

Claim 36. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said alcohol in (B)(1) is methanol.

Claim 37. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said sulfonic acid in (B)(2) is a C₄ to C₈ sulfonic acid.

Claim 38. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said sulfonic acid in (B)(2) is hexanesulfonic acid.

Claim 39. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said alkyl, hydroxyalkyl, and alkoxy groups, and one or both of alkyl and alkoxy portions of said alkoxyalkyl groups of said substituted benzoic acids in (B)(3) are C₁ to C₁₂.

Claim 40. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said alkyl and alkoxy groups, and one or both of alkyl and alkoxy portions of said alkoxyalkyl groups of said substituted benzoic acids in (B)(3) are branched.

Claim 41. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 40, wherein said branched alkyl and alkoxy groups

are selected from the group consisting of : i-propyl, 2-methylpropyl, t-butyl, and 2-methylbutyl.

Claim 42. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said substituted benzoic acid in (B)(3) is polysubstituted.

Claim 43. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 42, wherein said polysubstitution is with at least one of C₁ to C₁₂ unbranched and branched alkyl and alkoxy groups.

Claim 44. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein an alkoxy portion of an alkoxyalkyl group of said alkoxyalkyl substituted benzoic acid in (B)(3) is C₁ to C₆.

Claim 45. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 44, wherein said alkoxy portion of said alkoxyalkyl groups is selected from the group consisting of: methyloxy, ethyloxy, and propyloxy.

Claim 46. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 44, wherein said alkoxy portion is etherified with C₁ to C₄ hydroxyalkyl.

Claim 47. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 44, wherein said C₁ to C₄ hydroxyalkyl is selected from the group consisting of: hydroxymethyl, hydroxyethyl, and hydroxypropyl.

Claim 48. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein an amino group of said amino substituted benzoic acid in (B)(3) is alkylated.

Claim 49. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 48, wherein alkylation of said amino group is with a C₁ to C₄ alkyl group.

Claim 50. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said substituted benzoic acid in (B)(3) is selected from the group consisting of:

C₁ to C₆ alkyl, hydroxy-(C₁ to C₆)-alkyl, amino, and hydroxy substituted benzoic acids.

Claim 51. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said substituted benzoic acid in (B)(3) is an amino-substituted benzoic acid.

Claim 52. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 51, wherein said amino-substituted benzoic acid is aminobenzoic acid.

Claim 53. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 52, wherein an amino group of said aminobenzoic acid is one of: unsubstituted, and substituted.

Claim 54. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 52, wherein said substituted amino group of said aminobenzoic acid is one of: monosubstituted, and disubstituted.

Claim 55. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said alkyl substituted benzoic acid in (B)(3) is a monosubstituted or polysubstituted C₁ to C₄ alkyl benzoic acid.

Claim 56. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 55, wherein said polysubstituted C₁ to C₄ alkyl benzoic acid is tri-substituted.

Claim 57. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said hydroxyalkyl-substituted benzoic acid in (B)(3) is selected from the group consisting of: hydroxymethyl benzoic acid, hydroxyethyl benzoic acid, hydroxypropyl benzoic acid, and hydroxybutyl benzoic acid.

Claim 58. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said hydroxy-substituted benzoic acid is selected from the group consisting of: p-hydroxy benzoic acid, and m-hydroxy benzoic acid.

Claim 59. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said substituted benzoic acid in (B)(3) is selected

from the group consisting of: p-hydroxybenzoic acid, p-aminobenzoic acid, and trimethylbenzoic acid.

Claim 60. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 59, wherein said trimethylbenzoic acid is 2,4,6-trimethylbenzoic acid.

Claim 61. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said 5- and 6-member ring heterocyclic compound having at least one N or S atom in (B)(4) is selected from the group consisting of: pyridine, piperidine, pyrimidine, pyrrole, and thiophene.

Claim 62. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said unsubstituted and substituted 6-member ring heterocyclic compound having at least one N or S atom in (B)(4) is a pyridinecarboxylic acid.

Claim 63. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said unsubstituted and substituted 5-member ring heterocyclic compound having at least one N or S atom in (B)(4) is lipoic acid.

Claim 64. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said C₅ to C₁₀ oxocarboxylic acid in (B)(5) is selected from the group consisting of: 2-oxocarboxylic acid, 4-oxocarboxylic acid, 5-oxocarboxylic acid, and 9-oxocarboxylic acid.

Claim 65. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said C₅ to C₁₀ oxocarboxylic acid in (B)(5) is selected from the group consisting of: 5-oxopyrrolidine-2-carboxylic acid (pyroglutamic acid), levulinic acid, and oxo-dec-2-ene acid.

Claim 66. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein a C₂ to C₄ carboxylic acid of said phenyl-substituted and said phenoxy-substituted saturated C₂ to C₄ carboxylic acid in (B)(6) is selected from the group consisting of: acetic acid, propionic acid, and butyric acid.

Claim 67. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said aliphatic, aromatic, and heterocyclic C₂ to C₁₂ amino acid in (B)(7) is a monoaminomonocarboxylic acid, wherein an amino group is substituted with one of:

a C₂ to C₆ alkanoyl group, which is monosubstituted or polysubstituted with one selected from the group consisting of: hydroxy, C₁ to C₄ alkoxy, C₁ to C₄ hydroxyalkyl; and

a benzoyl group, which is monosubstituted or polysubstituted with one selected from the group consisting of: C₁ to C₄ alkyl, C₁ to C₄ alkoxy, C₁ to C₄ hydroxyalkyl, halogen, amino, and hydroxy.

Claim 68. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said aromatic amino acid in (B)(7) is a phenyl amino acid.

Claim 69. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 68, wherein said phenyl amino acid is selected from the group consisting of: phenylalanine, and tyrosine.

Claim 70. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said heterocyclic amino acid in (B)(7) is selected from the group consisting of: proline, hydroxyproline, and tryptophan.

Claim 71. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said aliphatic amino acid in (B)(7) is an aliphatic C₂ to C₆ monoaminomonocarboxylic acid.

Claim 72. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 71 wherein said amino group of said aliphatic C₂ to C₆ monoaminomonocarboxylic acid is substituted with one of: an acetyl group, and a benzoyl group.

Claim 73. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, having a molecular weight less than 800.

Claim 74. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said salt is a mixture of the reaction products of one of:

- I. one morphine alkaloid of formula I in (A), with one organic acid in (B);
- II. one morphine alkaloid of formula I in (A), with a plurality of organic acids in (B);
- III. a plurality of morphine alkaloids of formula I in (A), with one organic acid in (B); and

IV. a plurality of morphine alkaloids of formula I in (A), with a plurality of organic acids in (B).

Claim 75. (Currently Amended) ~~Morphine alkaloid acid addition salt~~ Composition according to claim 31, wherein said at least one organic acid in (B) is a pharmaceutically acceptable organic acid.

Claim 76. - (Cancelled)

Claim 77. - (Cancelled)

Claim 78. (Currently Amended) Composition according to claim ~~74 for transdermal administration~~ 31, further comprising a skin penetration enhancer.

Claim 79. (Previously Presented) Composition according to claim 78, wherein said skin penetration enhancer is selected from the group consisting of: a polyoxethylene sorbitane fatty acid, a polyoxethylene alcohol, and mixtures thereof.

Claim 80. (Currently Amended) Composition according to claim ~~74~~ 31, in a form selected from the group consisting of: lotion, ointment, cream, gel, aerosol spray, transdermal therapeutic system (TTS), transmucosal therapeutic system, and iontophoretic device.

Claim 81. (New) Composition according to claim 80, wherein said form is as a TTS.

Claim 82. (New) Composition according to claim 81, wherein said TTS comprises:

a backing layer, impermeable to said composition; and

a reservoir layer comprising:

40 - 80 wt% of a polymer material selected from the group consisting of: a polyacrylate, a polystyrene, and a silicone;

0.1 - 30 wt% of a plasticizer; and

0.1 to 30 wt% of said ~~morphine alkaloid acid addition salt~~
composition.

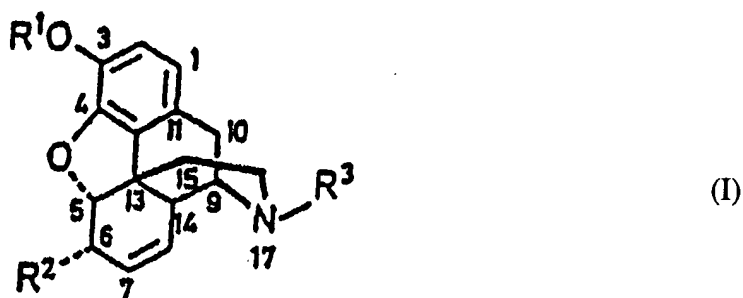
Claim 83. (Previously Presented) Composition according to claim 82, wherein said backing layer is a flexible or a non-flexible material.

Claim 84. (Previously Presented) Composition according to claim 82, wherein said backing layer is a composite material.

Claim 85. (Previously Presented) Composition according to claim 82, wherein material of said backing layer is selected from the group consisting of: polymer film, metal foil, polymer-coated metal foil, textile fabric impenetrable to components of said reservoir layer.

Claim 86. (Currently Amended) Method of forming a ~~morphine alkaloid acid addition salt~~, transdermal or transmucosal composition for administering at least one morphine alkaloid as a morphine acid addition salt, said method comprising the steps of:

A) providing a solution of a morphine alkaloid of formula I



where R¹ is selected from the group consisting of: H, and C₁ to C₆ alkyl;

R^2 is selected from the group consisting of: H, OH, $OC(O)CH_3$, $=O$, and $=CH_2$, such that when R^2 is H, OH, or $OC(O)CH_3$, a fourth valence bond at the C (6) position in formula I is H;

R^3 is selected from the group consisting of: CH_3 , cyclopropyl, cyclobutyl, and allyl;

the bond between the C (7) and C (8) positions in formula I is alternatively saturated; and

alternatively there is a nitroxyl group at the N (17) position in formula I; in an appropriate solvent therefor;

B) providing one of a liquid organic acid and a solution of an organic acid, selected from the group consisting of:

- 1) an acid that is an equilibrium product of a mixture of a monoester of a C_3 to C_{16} dicarboxylic acid and a monohydric C_1 to C_4 alcohol;
- 2) C_2 to C_{16} sulfonic acids;
- 3) a substituted benzoic acid selected from the group consisting of:
halogen, hydroxy, alkyl, hydroxyalkyl, alkoxy, alkoxyalkyl, and amino substituted benzoic acid;
- 4) 5- and 6-member ring heterocyclic compounds having at least one N or S atom, with unsaturated and saturated rings,

and unsubstituted, and substituted with one of: a carboxyl group, unbranched and branched carboxypropyl, and unbranched and branched carboxybutyl;

- 5) C_5 to C_{10} oxocarboxylic acids, unsaturated and saturated, and unsubstituted and substituted;
- 6) phenyl-substituted and phenoxy-substituted saturated C_2 to C_4 carboxylic acids; and
- 7) aliphatic, aromatic, and heterocyclic C_2 to C_{12} amino acids, and aliphatic, aromatic, and heterocyclic C_2 to C_{12} (mono) amino acids and (poly) amino acids (polypeptides), wherein at least one amino group is substituted with one of:
 - a) an unsubstituted C_2 to C_6 alkanoyl group,
 - b) a substituted C_2 to C_6 alkanoyl group,
 - c) an unsubstituted benzoyl group, and
 - d) a substituted benzoyl group;

C) reacting (A) and (B) to form said morphine alkaloid acid addition salt therefrom; ~~and~~

D) isolating said morphine alkaloid acid addition salt; and

- E) mixing said isolated morphine alkaloid acid addition salt with one of: a solvent for said morphine acid addition salt, and a suspension medium for said morphine acid addition salt;
said solvent or said suspension medium being selected from the group consisting of: glycerol, ethylene glycol, oleic acid, dimethylisobutylate, dimethylsulfoxide, and olive oil.

Claim 87. (Currently Amended) Method of forming a transdermal delivery system for a morphine alkaloid acid addition salt, comprising the steps of:

- A) forming and providing a ~~morphine alkaloid acid addition salt~~ transdermal composition for administering at least one morphine alkaloid as a morphine acid addition salt, according to the method of claim [[115]] 86;
- B) forming a mixture by mixing a therapeutically effective amount of said ~~morphine alkaloid acid addition salt~~ transdermal composition formed according to step (A), with components of a reservoir layer of said transdermal delivery system, said components comprising:
- a polymer material selected from the group consisting of:
rubber, synthetic homopolymers having rubber-like
properties, synthetic copolymers having rubber-like

properties, synthetic block polymers having rubber-like properties, polyacrylic acid esters, copolymers of polyacrylic acid esters, polyurethanes, and silicones;
a plasticizer;
a solvent; and
up to each of an additive selected from the group consisting of: tackifying agent, stabilizer, carrier, and filler;

- C) applying said mixture formed in (B) to a backing layer to form a matrix reservoir layer containing said ~~morphine alkaloid acid addition salt~~ transdermal composition therein on said backing layer;
- D) removing said solvent; and
- E) applying a protective layer to said matrix reservoir layer.